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Evidence-Based Clinical Guidelines for Chronic Diarrhea 2023

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Abstract

The Japan Gastroenterological Association (JGA) published the first version of clinical guidelines for chronic diarrhea 2023. These guidelines describe the definition, classification, diagnostic criteria, diagnostic testing methods, epidemiology, pathophysiology, and treatment of chronic diarrhea, and provide flowcharts for the diagnosis and treatment of chronic diarrhea based on the latest evidence. Treatment for chronic diarrhea begins by distinguishing secondary chronic constipation with a clear etiology, such as drug-induced diarrhea, food-induced diarrhea, systemic disease-associated diarrhea, infection-associated diarrhea, organic disease-associated diarrhea, and bile acid diarrhea. The first line of treatment for chronic diarrhea in the narrow sense, defined in these guidelines as functional diarrhea in routine medical care, is lifestyle modification and dietary therapy. The first medicines to be considered for oral treatment are probiotics for regulating the gut microbiome and antidiarrheals. Other medications, such as $5HT_3$ receptor antagonists, anticholinergics, Kampo medicine, psychotherapy, antibiotics, bulking agents, adrenergic agonists, and somatostatin analogues, lack sufficient evidence for their use, highlighting a challenge for future research. This Clinical Guidelines for Chronic Diarrhea 2023, which provides the best clinical strategies for treating chronic diarrhea in Japan, will also be useful for medical treatment worldwide.

Introduction

Diarrhea is one of the most common gastrointestinal symptoms encountered in everyday clinical practice. As distinguished from acute diarrhea caused by infectious diseases, chronic diarrhea has a high prevalence of approximately 5% [1,2] and significantly reduces quality of life. Despite its prevalence, Japan lacked clear clinical guidelines for chronic diarrhea. In response, the Japan Gastroenterological Association (JGA) decided to create the clinical guidelines for chronic diarrhea in January 2021. We present the first version of JGA evidence-based clinical guidelines for chronic diarrhea 2023. The guidelines were positively evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool [3]. The ratings of each domain are as follow: 58% for domain 1 (Scope and Purpose), 43% for domain 2 (Stakeholder Involvement), 47% for domain 3 (Rigour of Development), 60% for domain 4 (Clarity of Presentation), 42% for domain 5 (Applicability), and 58% for domain 6 (Editorial Independence). The overall rating is 54%.

Scope and purpose

These guidelines primarily aim to provide information that aids in decision-making regarding treatment policies and to improve the quality of life for patients with the common disease of chronic diarrhea. Accordingly, these guidelines organize and interpret currently available evidence and provide recommendations for making appropriate clinical decisions based on patient values. Furthermore, the guidelines are intended to help patients, their families, and medical professionals other than doctors involved in treating chronic diarrhea understand the outline of treatment for chronic diarrhea. In sharing the information in these guidelines, our goal is to provide a resource to help promote mutual understanding between medical professionals, patients, and their families in treating chronic diarrhea. According to decisions from the Guideline Development Committee, clinical questions were classified as follows.

・Background Question (BQ): For issues about which the conclusion is already clear and which past guidelines are in 100% agreement.

・Clinical Question (CQ): Major clinical issues. Questions that can determine recommendations and evidence-based standards through comprehensive literature searches and that influence the direction of medical treatment.

・Future Research Question (FRQ): Issues for which recommendations and evidence levels cannot be determined through a comprehensive literature search (sufficient evidence is not available, future research topics).

Questions established for these guidelines were 27: 10 CQ, 15 FRQ, and 2 BQ. The completed questions were categorized as follows: four addressed definition, classification, and diagnostic criteria (2 CQ, 1 FRQ, 1 BQ); five addressed diagnostic tests (3 CQ, 1 FRQ, 5 BQ); three addressed epidemiology (2 CQ, 1 FRQ); four addressed pathophysiology (1 CQ, 3 FRQ); and 11 addressed medical treatment (2 CQ, 9 FRQ).

Creation process

An evidence search was performed using a systematic method described in a previous report [4]. In short, we searched the PubMed electronic database for articles published in English from January 1983 to September 2021 and the Igaku Chuo Zasshi (ICHUSHI) database for articles published in Japanese. The evidence selection criteria were as follows: Initial assessment A: systematic review, meta-analysis, or randomized controlled trial (RCT); Initial assessment C: cohort study, or case-control study; Initial assessment D: case series, case report, and expert opinion. Multiple articles were collected from the literature, and their evidence levels were ranked based on bias risk and specific strengths. Quality of evidence was evaluated as: A: high-quality evidence, B: moderate quality evidence, C: low-quality evidence, and D: very low-quality evidence. Then, the strength of the recommendations was determined using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [5,6]. The strength of the recommendation was evaluated on four items: ① certainty (strength) of evidence, ② patient wishes, ③ benefit and harm, and ④ cost evaluation. Consensus was formed by voting using a modified Delphi method, and

decisions were made with 70% or more approval. If a conclusion could not be reached in the first round, the results were made public, and the voting was repeated after discussions considering the state of Japanese medicine. We determined recommendation strength as either a strong recommendation or an objection, or a weak recommendation or an objection, and created evidence-based statements and explanations for each CQ. After the final draft of the guidelines was evaluated by the guideline evaluation committee and modified, it was disclosed to the members of JGA, the Japanese Society of Gastroenterology, Japan Gastroenterological Endoscopy Society, and the Japan Society of Coloproctology. Furthermore, through discussions and public comments, these guidelines were completed. Adherence to the guideline will be monitored through the surveys conducted among healthcare providers by the Japanese Gastroenterological Association (JGA). Additionally, feedback on the usability and implementation of the guideline will be collected during core symposiums at the annual meetings held by the JGA. Regular clinical audits will be conducted under the supervision of the JGA. The guideline will be updated periodically based on the latest research findings and user feedback. The next update is expected to be overseen by the Japanese Society of Gastroenterology. Unfortunately, the patients' views and preferences could not be considered in this guideline development due to the absence of appropriate patient advocacy groups at present. Chronic diarrhea is a common disease, but not a rare disease.

Main text of the Japanese Chronic diarrhea guidelines

1. Definition, classification, and diagnostic criteria of Chronic diarrhea

CQ1-1. How is diarrhea defined? Furthermore, how is chronic diarrhea defined?

・Diarrhea is defined as "a condition in which the stool form is soft or watery and the frequency of defecation increases." Chronic diarrhea is defined as "a condition in which diarrhea that persists or recurs for four weeks or more causes various problems in daily life." (Recommendation; na, Evidence level B)

Comment: The condition of diarrhea is defined as "a condition in which the stool form is soft or watery and the frequency of defecation increases," and chronic diarrhea is defined as "a condition in which diarrhea that persists or recurs for four weeks or more causes various problems in daily life" [1,7-11]. The Bristol Stool Form Scale (BSFS) evaluates stool form [8]. A normal defecation frequency is between three times per week and two to three times per day [12], whereas diarrhea is defined as an increased defecation frequency of three or more times per day [9,11]. Moreover, the chronic period is defined as 4 weeks or more because intestinal infections, the most common cause of acute diarrhea, typically resolve in 1 week or 4 weeks at the most [1]. However, the disease chronic diarrhea is a condition where diarrhea persists or recurs for 4 weeks or more, causing symptoms such as frequent bowel movements, feelings of defecation urgency, fecal incontinence, and abdominal pain [11], which interfere with activities of daily life, such as schoolwork, employment, and sleep, and requires examination, diet/lifestyle guidance, or drug treatment. These guidelines used an expanded interpretation of functional diarrhea in line with routine clinical practice to define chronic diarrhea in the "narrow sense." These diagnostic criteria are based on functional diarrhea as defined in Rome IV [13]. However, the Rome IV criteria's definition of chronic as "a condition that started more than 6 months ago and has met the respective criteria for the past 3 months" is not necessarily suitable for daily clinical practice, so it was set at 4 weeks or more for daily clinical practice. Furthermore, functional diarrhea and diarrhea-predominant irritable bowel syndrome (diarrhea-predominant IBS) are considered to be on a continuum of diseases, so considering the diversity of daily clinical practice, if chronic diarrhea is the cardinal symptom, it was decided not to inquire about accompanying symptoms such as abdominal pain.

CQ1-2. How is chronic diarrhea classified?

・Chronic diarrhea is classified into eight categories: (1) drug-induced diarrhea, (2) food-induced diarrhea, (3) systemic disease-associated diarrhea, (4) infection-associated diarrhea, (5) organic disease-associated diarrhea (inflammatory or neoplastic), (6) bile acid diarrhea, (7) functional diarrhea, (8) diarrhea-dominant irritable bowel syndrome.

(**Recommendation; n.a., Evidence level C**)

Comment: Classification of chronic diarrhea is based on stool characteristics, pathophysiology, and etiology. Although distinguishing between watery, fatty, bloody, and purulent diarrhea is important for classification based on stool characteristics [14, 15], the reality is that it is difficult for non-specialists to grasp the overall picture because classification cannot be performed without a stool test. The American Gastroenterological Association (AGA) guidelines categorize diarrhea into drug-induced, food-induced, systemic disease-associated, infection-associated, and functional diarrhea/diarrhea-dominant IBS (IBS-D) [1] and list blood tests, physiological tests, stool tests, culture tests, imaging tests, and other methods for distinguishing between systemic disease-associated, infection-associated, organic disease-associated (inflammatory bowel disease, celiac disease, neoplastic disease, etc.), and bile acidic diarrhea [16-18]. Bile acidic diarrhea is further classified into three types [19]. Bile acid diarrhea is diagnosed with abnormal selenium-75-homocholic acid taurine (^{75}SeHCAT) scan, increased serum 7a-hydroxy-4-cholesten-3-one (C4), and/or decreased serum fibroblast growth factor 19 (FGF-19), which positive response to administration of bile acids sequestrants (e.g. cholestyramine or colesevelam) are often substituted for, depending on the countries [19]. Careful diagnosis and interviews are important because many older people are taking drugs that contribute to diarrhea. It should also be noted that fecal incontinence is also important for differential diagnoses.

BQ1-1. What are the diagnostic criteria for chronic diarrhea?

- The diagnostic criterion for chronic diarrhea is "a condition in which loose or watery stools persist or recur for four weeks or more."

Comment: This complies with the 2016 Rome IV diagnostic criteria for "functional diarrhea" [13] as well as the diagnostic criteria in the chronic diarrhea treatment guidelines announced by the British Gastroenterological Association in 2018 [8] and AGA in 2019 [17]. The duration of four weeks or more is set to rule out the possibility of infection-associated diarrhea. Stool form was defined using the BSFS because it is necessary to understand abnormal stool shape rather than frequency when assessing diarrhea. These guidelines exclude chronic diarrhea cases resulting from other causes, such as organic diseases. Chronic diarrhea is the cardinal symptom if soft or watery stools account for 25% or more of bowel movements. A diagnosis of chronic diarrhea in the narrow sense will be made, regardless of whether abdominal pain is present (this mainly indicates functional diarrhea, but in daily clinical practice, the chronic period is four weeks or more). Chronic diarrhea (narrow sense) does not explicitly include IBS-D. However, it does include patients who have not yet been definitively diagnosed with IBS-D and patients with IBS-D who have transitioned to mainly diarrhea in the course of their disease (Table 1).

FRQ1-1. How is refractory chronic diarrhea defined?

・There are no studies that have strictly defined refractory chronic diarrhea, making this a topic for future investigation.

Comment: Cases that do not respond to common diarrheal treatments and chronic diarrhea that recurs despite adequate treatment are thought to fall under the "refractory chronic diarrhea" category, but no studies have defined this term. In real-world clinical practice, attention must be paid to the fact that not only disease activity but also patient factors (comorbidities, treatment preferences, economic factors, regional characteristics, etc.) and medical provider factors (lack of knowledge and experience, biased drug selection, lack of patient communication) are associated with treatment resistance [20,21]. In the future, we hope to study the factors related to the severity and refractoriness of functional diarrhea.

2. Diagnostic tests

FRQ2-1. What medical questionnaires are useful in chronic diarrhea treatment?

・Currently, no specialized medical questionnaires for chronic diarrhea have been established to be useful in Japan.

Comment: Many questionnaires have been devised to evaluate diarrheal symptoms, but most of them have been designed to assess the effects of IBS-D on quality of life [22] and secondary diarrhea caused by other diseases such as acute enterocolitis, antibiotics, or anticancer drug treatment [23]. Although diarrheal symptoms are evaluated as a component of questionnaires for general functional gastrointestinal disorders in such questionnaires, there was only one questionnaire in this study that specifically evaluated diarrheal symptoms [24]. In the future, we expect new Japanese questionnaires to be created or those prepared overseas to be translated and their validity evaluated for improving the quality of treatment for chronic diarrhea.

BQ2-1. What physical examinations are useful in clinical management of chronic diarrhea?

・In clinical management of chronic diarrhea, it is essential to discern the primary disease, so useful physical examinations include general condition/skin examination, craniocervical examination, abdominal/anal examination, and stool observation.

Comment: Although studies on the usefulness of specific physical examinations in the clinical management of chronic diarrhea are few, and currently, it is difficult to make an evaluation based on sufficient evidence, in daily clinical practice, it is nevertheless important to pay attention to physical findings in addition to abdominal symptoms, as this leads physicians to select and perform appropriate tests for differential diagnosis from a wide range of test items [25]. It is reported to be useful in classifying diarrhea and narrowing down a diagnosis before testing because the primary diseases causing chronic diarrhea are diverse and wide-ranging [26]. We suggest including a physical examination, and a medical interview when examining patients for chronic diarrhea is important.

CQ2-1. What are the warning symptoms and indications of chronic diarrhea? Also, are the warning symptoms and indications effective?

Warning symptoms and indications of chronic diarrhea include unexpected weight loss, nocturnal diarrhea, recent use of antibiotics, bloody stools, frequent or profuse diarrhea, undernutrition, and a family history of inflammatory bowel disease or colorectal cancer. However, their usefulness is unclear. (Recommendation; n.a., Evidence level C)

Comment: If the above warning symptoms and indications are observed in a patient with chronic diarrhea, further testing is required, but even if they are not observed, it is important to proceed with the treatment of chronic diarrhea by conducting a detailed medical history focused on diarrhea symptoms, physical examination, and minimal tests [1]. In other words, although checking for warning symptoms and indications to differentiate organic disease-associated diarrhea from chronic diarrhea (narrow sense) has been proposed, the usefulness of these warning symptoms and indications is not clear, and future research is needed [27].

CQ2-2. What laboratory tests (other than endoscopy) are useful in the differential diagnosis of chronic diarrhea?

・There are blood, fecal, and imaging tests; the underlying disease and pathophysiology are examined from the interview and physical examination, and necessary tests are determined and carried out individually. (Strong recommendation, Evidence level A, 90% agreed)

Comment: Blood tests measure complete blood count, electrolytes, CRP, ALB, and urea nitrogen [8]. Malabsorption syndrome is likely to cause anemia, hypoproteinemia, and hypolipidemia because of iron, VB12, and folic acid deficiencies. Thyroid function tests (free T3, free T4, TSH) should be performed to differentiate hyperthyroidism. Consider the differential diagnosis of *Clostridioides difficile* infection in patients with a history of antibiotic use, stool culture in patients suspected of

bacterial enterocolitis, fecal egg testing, and direct microscopic examination for parasitosis [18]. Fecal occult blood testing is used to screen for neoplastic diseases in older people and IBD in young people. Fecal calprotectin (and lactoferrin) are elevated in IBD and are useful in differentiating it from IBS [28]. Abdominal CT tests (and MRI tests) are used to identify intestinal lesions in inflammatory and neoplastic diseases and to diagnose the presence of extra-intestinal lesions such as exocrine pancreatic insufficiency and neuroendocrine tumors associated with pancreatic diseases [8]. However, these tests show no abnormalities for bile acid diarrhea and small intestinal bacterial overgrowth (SIBO), so specific tests are required [8,29,30].

CQ2-3. What is the significance of endoscopy in the differential diagnosis of chronic diarrhea?

・Colonoscopy is recommended for chronic diarrhea because it is useful in differential diagnosis and helps exclude organic diseases. (Strong recommendation, Evidence level A, 100% agreed）

・We recommend performing random biopsies even if no endoscopic abnormalities are found, to account for potential risks. (Weak recommendation, Evidence level B, 77% agreed）

Comment: Colonoscopy for chronic diarrhea is useful in diagnosing and excluding organic diseases [1]. Given that endoscopy and random biopsies have been reported to show abnormal findings in 17-28% of patients with chronic diarrhea who meet Rome IV criteria [31], it is recommended to be performed particularly in empiric therapy-resistant cases, patients over the age of 50, and patients with warning indications [1,13]. Furthermore, to exclude diseases that require biopsy for diagnosis, such as microscopic colitis (lymphocytic colitis, collagenous colitis), eosinophilic gastroenteritis, and amyloidosis, it is recommended that random biopsies should be taken throughout the large intestine, to account for potential risk of biopsy [32].

3. Epidemiology

CQ3-1. What is the prevalence of chronic diarrhea (narrow sense)?

・The prevalence of chronic diarrhea (narrow sense) among Japanese people is estimated to be around 3-5%, and it tends to be more common among men. (Recommendation; n.a., Evidence level B)

Comment: Past studies have shown the prevalence of chronic diarrhea that lasts for more than four weeks to be 1.0-6.6%, with an etiology more diverse than that of acute diarrhea [8,33,34]. In Europe and America, the prevalence of chronic diarrhea has been reported at 4-5% [35]. As defined in these guidelines, chronic diarrhea mostly corresponds to the Rome IV criteria for functional diarrhea. An internet survey using the Rome IV criteria conducted in 33 countries worldwide found the prevalence of functional diarrhea to be 4.7%, while in Japan, it was 5.2% [2]. However, there is little evidence for research on chronic diarrhea, making it difficult to evaluate because it varies depending on the definition and subject.

CQ3-2. Does chronic diarrhea (narrow sense) reduce QOL?

・Chronic diarrhea (narrow sense) may reduce QOL and labor productivity. (Recommendation; n.a., Evidence level D)

Comment: Compared to patients with IBS-D, patients with functional diarrhea have been reported to complain of anxiety, depressive symptoms, and sleep disturbances, even though their abdominal pain and diarrhea are less severe [36]. A study comparing IBS patients with the general population of the US showed that IBS patients had a lower QOL [37], and a study by Kanazawa et al. in Japan also showed that IBS patients' QOL was lower than that of healthy subjects [38]. It has also been shown that the labor productivity of people with chronic diarrhea declines significantly, with an annual economic loss upwards of $136 million [34]. These results suggest that chronic diarrhea reduces QOL and labor productivity, but studies from Japan are limited and based on little evidence.

FRQ3-1. Does chronic diarrhea (narrow sense) affect long-term prognosis?

・Although no clear evidence that chronic diarrhea (narrow sense) affects long-term prognosis has been found, the details are unclear because the literature is insufficient.

Comment: Studies discussing the effects of chronic diarrhea (narrow sense) on long-term prognosis are few, and in Japan, there have been no investigations of long-term prognosis related to chronic diarrhea (narrow sense). Many cases of chronic diarrhea (narrow sense) have a good prognosis and are medically treatable, and there is no clear evidence that chronic diarrhea leads to death. However, a meta-analysis evaluating the long-term course of hemolytic uremic syndrome (HUS) associated with diarrheal symptoms (mostly acute diarrhea, but including some chronic diarrhea) confirmed that approximately 12% of patients died [39], but this was a study of the long-term prognosis and acute diarrhea, with evidence for chronic diarrhea (narrow sense) expected to accumulate in the future.

4. Pathophysiology

FRQ4-1. What is the pathophysiology that causes chronic diarrhea (narrow sense)?

・Though studies on chronic diarrhea (narrow sense) are few, various pathophysiologies have been proposed for IBS-D, which is considered to be on a continuous spectrum.

Comment: Mechanisms that cause diarrhea in IBS-D include: abnormalities in water absorption mechanisms [40,41]; microinflammation in the digestive tract [42-44]; mucosal barrier dysfunction [45]; abnormalities in hormones, amines, and peptides [46-49]; malabsorption of bile acid [30]; abnormalities in short-chain fatty acids [50]; intestinal motility disorders [51]; malabsorption of dietary components [52]; abnormalities of the autonomic nervous system [53]; genetic factors [54,55]; psychological abnormalities (FRQ4-02), lifestyle habits (CQ4-01), and intestinal bacteria abnormalities (FRQ4-03) (Table 2). Meanwhile, there are few reports of chronic diarrhea, and the pathophysiology is unclear.

FRQ4-2. Do psychological abnormalities contribute to the pathophysiology of chronic diarrhea (narrow sense)?

・There is no clear evidence showing a relationship between psychological abnormalities and the pathophysiology of chronic diarrhea (narrow sense).

Comment: There are many reports that psychological abnormalities are involved in the pathophysiology of IBS. Studies have shown that depression and anxiety are risk factors for the onset of IBS [111, 112], that the prevalence of bipolar disorder is high in IBS patients [113], and that IBS is often accompanied by sleep disorders [114]. However, no direct reports on the relationship between psychological abnormalities and patients with only IBS-D are lacking. In contrast, no reports indicate a relationship between chronic diarrhea in the narrow sense (mainly functional diarrhea) and psychological abnormalities, and there is currently no evidence of a relationship between the two.

CQ4-1. Does lifestyle habits play a role in the pathophysiology of chronic diarrhea (narrow sense)?

- Dietary content contributes to the pathophysiology of chronic diarrhea (narrow sense).

・It is unclear whether lifestyle habits other than diet are involved in the pathophysiology of chronic diarrhea (narrow sense).

(Recommendation; n.a., Evidence level B）

Comment: Excessive consumption of beverages containing fructose, caffeine, or foods containing xylitol may worsen diarrhea [115]. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), which are difficult to digest and absorb in the small intestine, ferment in the large intestine to produce gas. Additionally, the osmotic concentration gradient increases the water in the small intestine, stimulating the intestinal tract to expand and causing pain, diarrhea, and loose stool symptoms because of intestinal overhydration. A low FODMAP diet has been reported to improve symptoms of IBS-D [116]. While irregular eating habits and lack of exercise may be associated with symptoms of functional diarrhea [117], the association with smoking and alcohol consumption varies between studies, requiring further investigation.

FRQ4-3. Are intestinal bacteria involved in the pathophysiology of chronic diarrhea (narrow sense)?

・There is a possibility that the intestinal bacteria are involved in the pathophysiology of chronic diarrhea (narrow sense).

Comment: A significant decrease in *Eubacterium rectale*, *Bacteroides*, *Faecalibacterium prausnitzii*, the main indigenous bacteria in stool, was observed in patients with chronic diarrhea as compared to healthy people, as was an increase in the relatively scarce indigenous bacteria *Bifidobacterium*, *Eubacterium cylindroides*, *Clostridium histolyticum*, and *Clostridium lituseburense* [118]. A systematic review of intestinal bacteria in IBS patients showed significant declines in the *Bifidobacterium* and *Faecalibacterium* genera in IBS-D patients compared to healthy subjects [119]. Whether these changes in the gut microbiome are a cause or a consequence of diarrhea is not fully understood, and further research is required. Given that probiotics and fecal transplantation may be effective against IBS symptoms [120,121], it is plausible that abnormal intestinal flora may cause chronic diarrhea.

5. Treatments

FRQ5-1. Is lifestyle modification effective for chronic diarrhea (narrow sense)?

・Although there is little evidence to support this, lifestyle modification may be effective for chronic diarrhea (narrow sense).

Comment: No studies have examined whether lifestyle modification is effective for chronic diarrhea (narrow sense). However, research has been conducted on whether lifestyle habits contribute to the pathophysiology, with studies showing that chronic diarrhea is associated with increased daily carbohydrate intake [122], lack of exercise on holidays, and irregular eating habits [117]. Although there is little evidence demonstrating the effectiveness of lifestyle modification for chronic diarrhea, we recommend that it be undertaken with the understanding that the evidence is uncertain but that implementing it has no disadvantage.

CQ5-1. Are probiotics effective for chronic diarrhea (narrow sense)?

・Probiotics may be effective for chronic diarrhea (narrow sense). However, there is no clear evidence regarding the effective bacterial species, dosage, or duration of administration.

Comment: Often sold as supplements or pharmaceuticals, “probiotics” refer to live bacteria that benefit humans by improving the balance of intestinal bacteria, drugs, or foods containing those microorganisms. The clinical effectiveness of probiotics has been reported in the treatment of IBS-D, antibiotic-associated diarrhea, intestinal infections, and chemoradiotherapy-induced diarrhea [123]. Although not highly recommended in the British guidelines, as a treatment for IBS in particular, the validity of probiotics has been shown because of their effectiveness in improving symptoms and the low incidence of adverse events [124], and they are also highly recommended in clinical guidelines for IBS 2020 from the Japan Society of Gastroenterology [125]. Although probiotics' symptom improvement and anti-inflammatory effects on chronic diarrhea have recently been reported [126], details on what mechanisms and which bacterial species are effective remain subjects for further investigation.

CQ5-2. Are antidiarrheal drugs effective for chronic diarrhea (narrow sense)?

・Loperamide hydrochloride is the most commonly used and effective drug for relieving symptoms of chronic diarrhea (narrow sense). (Recommendation; n.a., Evidence level C)

Comment: Loperamide hydrochloride is the most commonly used antidiarrheal drug in clinical practice, and it has been shown to control stool consistency in patients with chronic diarrhea [127], while loperamide oxide has been shown to reduce the weight of moist stool and improve patient symptoms [128]. Additionally, loperamide hydrochloride is effective in alleviating symptoms such as bile acid diarrhea [129], chronic radiation enteritis characterized primarily by diarrhea symptoms [130], and chemoradiotherapy-induced diarrhea [131]. These findings show that the administration

of loperamide hydrochloride is effective as a first-choice for alleviating symptoms of chronic diarrhea.

FRQ5-2. Are serotonin (5-HT_3) receptor antagonists effective for chronic diarrhea (narrow sense)?

・There is no evidence regarding the effect of 5-HT_3 receptor antagonists on chronic diarrhea (narrow sense). The effectiveness of 5-HT_3 receptor antagonists for chronic diarrhea (narrow sense) is unclear. (Recommendation; n.a., Evidence level C）

Comment: There is little evidence supporting the involvement of 5-HT_3 in the pathophysiology of patients with chronic diarrhea (narrow sense), and there are no reports examining the efficacy of 5-HT_3 receptor antagonists. However, 5-HT_3 receptor antagonists have been reported to alleviate abdominal pain and discomfort in IBS-D and improve defecation urgency, frequency, and stool form [132,133]. Functional diarrhea and IBS-D are considered to be on a continuum of pathological conditions with different phenotypes [19, 36]. As with IBS-D patients, while 5-HT_3 receptor antagonists may be effective for some chronic diarrhea (narrow sense) patients, large-scale clinical studies are required to evaluate their validity and effectiveness.

FRQ5-3. Are anticholinergic drugs effective for chronic diarrhea (narrow sense)?

・There is no evidence regarding the effects of anticholinergic drugs on chronic diarrhea (narrow sense). The effectiveness of anticholinergic drugs for chronic diarrhea (narrow sense) is unknown.

Comment: There is little or no research on the effectiveness of anticholinergic drugs for chronic diarrhea (narrow sense). Although there are relatively many studies on the effectiveness of anticholinergic drugs for IBS, data showing their effects on diarrheal symptoms is extremely limited. Though a meta-analysis showed that otilonium bromide effectively improves global symptoms in IBS patients, its effect on diarrheal symptoms is unclear [134]. In addition, the results of two RCTs on otilonium bromide were inconsistent regarding its effects on diarrheal symptoms in IBS patients [135,136]. Cimetropium bromide reduced the severity score of diarrheal symptoms in IBS by approximately 50%, but no statistically significant difference was observed compared with placebo [137].

FRQ5-4. Is Kampo medicine effective for chronic diarrhea (in a narrow sense)?

・The effectiveness of Kampo medicines for chronic diarrhea (narrow sense) is unknown.

Comment: The elixir called “keishi-ka-shakuyaku-to” has analgesic and antispasmodic effects, suppresses intestinal spasms, and improves defecation symptoms, including abdominal pain and diarrhea. Additionally, the known pharmacological effects of the elixir “hange-shashin-to” include increasing water absorption in the large intestine and inhibiting intestinal peristalsis, which improves diarrheal symptoms. It is possible that Kampo medicines, because of their mechanism of action, are effective against chronic diarrhea (narrow sense). However, the evidence level is insufficient, and further investigation is required.

FRQ5-5. Is psychotherapy effective for chronic diarrhea (narrow sense)?

・The efficacy of psychotherapy for chronic diarrhea (narrow sense) is unknown.

Comment: There are no reports of studies in which psychotherapy was implemented for chronic diarrhea (narrow sense) [19]. It has been reported that acute stress accelerates transit through the digestive tract [138], but the relationship between chronic stress and functional diarrhea is unclear [19]. Further, since the psychological characteristics of functional diarrhea are not thought to be involved in the same way as those of IBS-D, psychotherapy for chronic diarrhea (narrow sense) cannot be expected to be as useful as for IBS, and therefore is thought to be limited. While there are no reports examining the effects of psychotherapy on chronic diarrhea (narrow sense) in detail, functional diarrhea, an academic diagnosis of chronic diarrhea (narrow sense), and IBS-D, though academically diagnosed differentially, are thought to be pathophysiologies on a continuum with different phenotypes. Therefore, there may be cases where psychotherapy has been effectively used to treat chronic diarrhea (narrow sense) and require further investigation.

FRQ5-6. Are antibiotics effective for chronic diarrhea (narrow sense)?

・The efficacy of antibiotics for chronic diarrhea (narrow sense) is unknown.

Comment: There are no reports of studies examining the effects of antibiotics on chronic diarrhea (narrow sense) [19]. Clinical guidelines for functional bowel disorders with diarrhea as the main symptom, jointly published by the European Society of Gastrointestinal Endoscopy and the European Society of Neurogastroenterology & Motility, recommend the use of rifaximin, a non-absorbable antibiotic, in IBS-D. However, the additional effect compared to placebo was not large, and there was little evidence of its effectiveness against functional diarrhea, an academic diagnosis of chronic diarrhea (narrow sense) [139].

Functional diarrhea and IBS-D are regarded as continuous pathophysiological conditions with different phenotypes, meaning they can transition from one into the other depending on the time, even in the same case, so while there are likely cases where antibiotics were effective against chronic diarrhea (narrow sense), this remains a topic for future investigation.

FRQ5-7. Are bulking agents effective for chronic diarrhea (narrow sense)?

・The efficacy of bulking agents for chronic diarrhea (narrow sense) is unknown.

Comment: One bulking agent is calcium polycarbophil, a macromolecular polymer. It is not absorbed by the gastrointestinal tract; instead, it swells and forms a gel as it absorbs water in the intestines and is then excreted. Currently, no reports demonstrate the usefulness of calcium polycarbophil for functional diarrhea, which is an academic diagnosis for chronic diarrhea (in a narrow sense). Calcium polycarbophil is useful for IBS in a randomized controlled overseas trial [140]. Functional diarrhea and IBS-D are considered to be continuous pathophysiological conditions with different phenotypes, meaning they can transition from one into the other depending on the time, even in the same case, so there may be cases in which bulking agents are effective against functional diarrhea. However, because of insufficient evidence, no conclusions can be drawn now.

FRQ5-8. Are adrenergic agonists effective for chronic diarrhea (narrow sense)?

・The effectiveness of adrenergic agonists for patients with chronic diarrhea (in a narrow sense) is unknown.

Comment: No evidence has been reported to recommend adrenergic agonists in patients with chronic diarrhea (narrow sense). In animal experiments, it has been reported to be effective in improving diarrhea [141]. In a placebo-controlled study in healthy subjects, α2-receptor agonist clonidine effectively increased colonic compliance, reduced sensations of tightness and abdominal gas, pain, and rectal urgency, and prolonged intestinal transit time [142]. Additionally, administering clonidine to patients with IBS-D was shown to improve their symptoms [143].

FRQ5-9. Are somatostatin analogs effective for chronic diarrhea (narrow sense)?

・Somatostatin analogs may effective for chronic diarrhea (narrow sense). However, the evidence is limited, indicating a need for future investigation.

Comment: Somatostatin analogs inhibit intestinal motility and water-electrolyte transport [141,144]. Although few trials have examined their effects on chronic diarrhea (narrow sense), a Belgian prospective trial that tested lanreotide acetate showed improvement in 42.4% of patients [145]. Many trials have been conducted broadly for chronic diarrhea, and meta-analyses have shown the effectiveness of somatostatin analogs. However, caution is needed as the efficacy varies depending on the target disease [146,147]. Somatostatin analogs including octreotide acetate, lanreotide acetate, and pasireotide pamoate are approved for acromegaly, neuroendocrine tumors, but not for chronic diarrhea in Japan. Somatostatin analogs may be effective against chronic diarrhea (narrow sense), but the evidence is insufficient.

6. Flowcharts of clinical practice for chronic diarrhea

Based on the 10 CQs, 15 FRQs, and 2 BQs outlined in the guideline, we have constructed the flowcharts for clinical practice in managing chronic diarrhea. The first flowchart includes the initial medical treatment strategy of chronic diarrhea (Fig. 1). Initially, the patients with chronic diarrhea are assessed through medical interviews, physical findings, blood tests. Drug-induced diarrhea and food-induced diarrhea are differentiated. Subsequent studies including stool examinations, computed tomography, colonoscopy, and esophagogastroduodenoscopy are conducted to rule out systemic disease-associated diarrhea, infection-associated diarrhea, organic disease-associated diarrhea. Bile acid diarrhea is then excluded. The remaining patients are likely diagnosed with functional diarrhea or diarrhea-predominant IBS. Second flowchart includes the medical treatment strategy for chronic diarrhea (narrow sense) (Fig. 2), Initially, improvement in lifestyle habits and continuation of dietary therapy are recommended. If these prove ineffective, probiotics and antidiarrheal medications are administered. Should these have a poor response, the possibility of secondary chronic diarrhea should be reconsidered. Once secondary chronic diarrhea is ruled out, treatment options include $5HT_3$ receptor antagonists, anticholinergics, Kampo medicines, psychotherapy, antibiotics, bulking agents, adrenergic agonists, somatostatin analogues, although their efficacy may be unclear.

Apendix

The members of the Guidelines Committee who created and evaluated the Japanese Gastroenterological Association ‘‘Evidence-based clinical guidelines for chronic diarrhea 2023’’ are listed below.

Creation committee

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Conflict of Interest Statement
The following were the competing interests of guideline development committee members, guideline committee members, and guideline evaluation committee members. Any financial relationship with enterprises, businesses or academic institutions in the subject matter or materials discussed in the manuscript are as follows: (1) those from which the authors, the spouse, partner or immediate relatives of the authors have received individually any income, honoraria or any other type of remuneration; Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company, EA Pharma Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., AstraZeneca K. K., Olympus Corporation, JIMRO Co., Ltd., AbbVie GK, KYORIN Pharmaceutical Co., Ltd., Viatris Inc., Astellas Pharma Inc., Gilead Sciences, Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K. K., Tsumura & Co., Towa Pharmaceutical Co., Ltd., Bristol-Myers Squibb K. K., Kowa Pharmaceutical Co., Ltd., Taisho Pharmaceutical Holdings Co., Ltd., Biofermin Pharmaceutical Co., Ltd., Mylan EPD G. K., Daiichi Sankyo Inc., Zeria Pharmaceutical Co., Ltd., and (2) those from which the authors have received research grant; AbbVie GK, GlaxoSmithKline K. K., Janssen Pharmaceutical K. K., EA Pharma Co., Ltd., Fujifilm Corporation, Mochida Pharmaceutical Co., Ltd., Aska Pharmaceutical Co., Ltd., Astellas Pharma Inc., Gilead Sciences, Inc., Biofermin Pharmaceutical Co., Ltd., Mylan EPD G. K., Tsumura & Co., Zespri International Limited, and (3) those from which the authors have received scholarship; Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Tobishima Kodomo Clinic, Takeda Pharmaceutical Company, Daiichi Sankyo Inc., AbbVie GK, Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb K. K., EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K. K. and (4) those from which the authors have received individually endowed chair; Ono Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Otsuka Pharmaceutical Factory, Inc., Fujifilm Medical Co., Ltd., Terumo Corporation, FANCL Corporation, Ohga Pharmacy, Abbott Japan LLC, and Muta Hospital.

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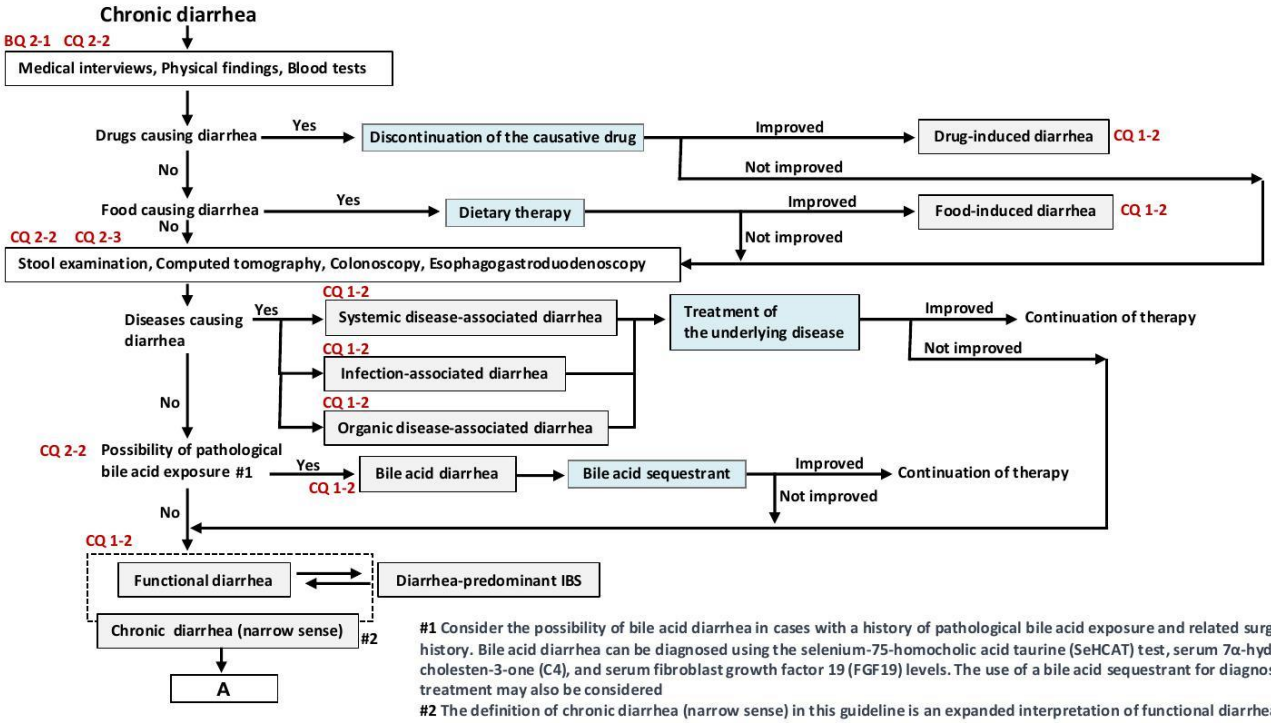
Figure Legends

Fig. 1 Initial medical treatment strategy for chronic diarrhea

First, the patients with chronic diarrhea are assessed through medical interviews, physical findings, blood tests. Drug-induced diarrhea and food-induced diarrhea are differentiated. Subsequent studies including stool examinations, computed tomography, colonoscopy, esophagogastroduodenoscopy were conducted to rule out systemic disease-associated diarrhea, infection-associated diarrhea, organic disease-associated diarrhea. Bile acid diarrhea is then excluded. The remaining patients are likely diagnosed with functional diarrhea or diarrhea-predominant IBS. This guideline defines chronic diarrhea in a narrow sense. IBS; irritable bowel syndrome

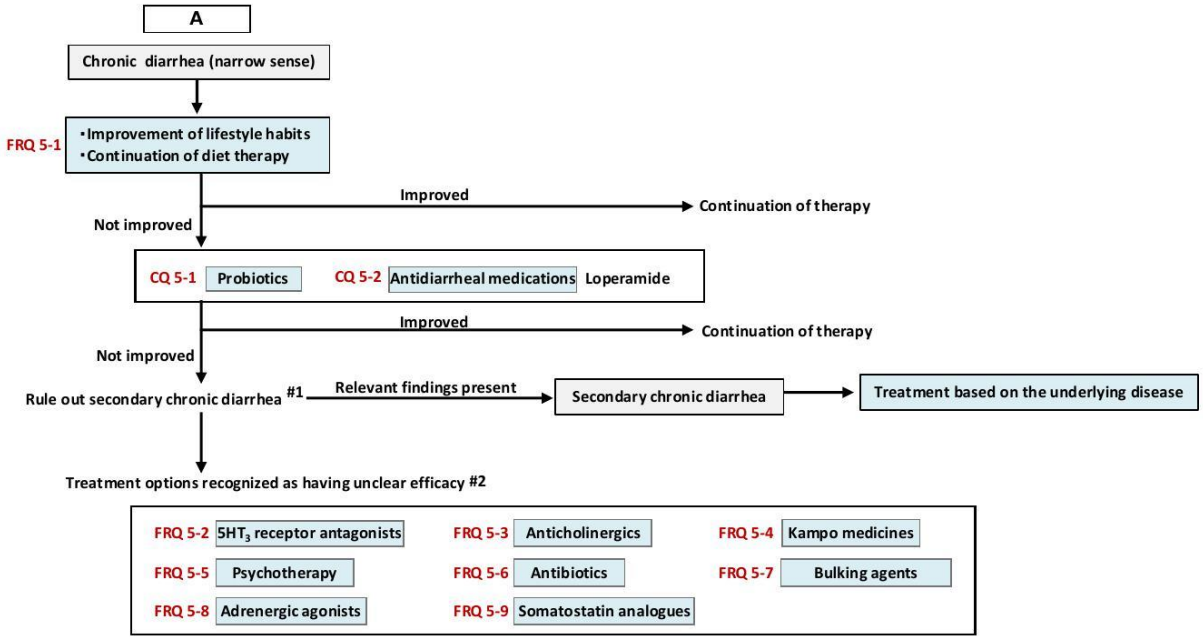
Fig. 2 Medical treatment strategy for chronic diarrhea (narrow sense)

Initially, improvement in lifestyle habits and continuation of dietary therapy are recommended. If these prove ineffective, probiotics and antidiarrheal medications are administered. Should these have a poor response, the possibility of secondary chronic diarrhea should be reconsidered. Once secondary chronic diarrhea is ruled out, treatment options include $5HT_3$ receptor antagonists, anticholinergics, Kampo medicines, psychotherapy, antibiotics, bulking agents, adrenergic agonists, somatostatin analogues, although their efficacy may be unclear.



#1 Consider the possibility of bile acid diarrhea in cases with a history of pathological bile acid exposure and related surgical history. Bile acid diarrhea can be diagnosed using the selenium-75-homocholic acid taurine (SeHCAT) test, serum 7α-hydroxy-4-cholesten-3-one (C4), and serum fibroblast growth factor 19 (FGF19) levels. The use of a bile acid sequestrant for diagnostic treatment may also be considered

#2 The definition of chronic diarrhea (narrow sense) in this guideline is an expanded interpretation of functional diarrhea adapted to general clinical practice. Chronic diarrhea (narrow sense) does not actively include diarrhea-predominant IBS (IBS-D), but it does encompass patients who are in the process of being diagnosed with IBS-D.



#1 Drug-induced diarrhea; Food-induced diarrhea; Systemic disease-associated diarrhea; Infection-associated diarrhea; Organic disease-associated diarrhea, and Bile acid diarrhea will be differentiated as secondary chronic diarrhea.
#2 Differential diagnosis of secondary chronic diarrhea is reconsidered when there is no improvement

Table 1 Diagnostic criteria for chronic diarrhea

Diagnostic criteria for "chronic diarrhea"
a. Loose or watery stools for change in stool shape
b. The change has been persistent or recurring for more than 4 weeks
Diagnostic criteria for "narrow-sense chronic diarrhea"
c. Criteria a and b are met d. Other causes such as organic diseases have been excluded e. More than 25% of bowel movements are loose or watery stools, regardless of the presence or absence of abdominal pain.

Table 2. Proposed mechanisms underlying diarrhea-predominant irritable bowel syndrome and chronic diarrhea (narrow sense)

Mechanism	Related factors	Pathogenesis in IBS-D/chronic diarrhea
Alteration of water transport	Water channel aquaporin (AQP)	AQP3↓、AQP7↑、AQP8↑ [40]
	Cystic fibrosis transmembrane conductance regulator (CFTR) Calcium-activated chloride channels	Improvement of symptoms by treatment of crofelemer [41]
Low-grade gastrointestinal inflammation	Mast cell invasion	Increased number of mucosal mast cells in the jejunum [56-58], ileum [59,60], colon [42,59,61-67], and rectum [59] Improvement of symptoms by treatment of cromolyn [44]
	Chemical mediators from mast cells	Increased production of tryptase [42,44,58,61-64,67], histamine [42,61,62,64,68], prostaglandin E_2 [61,69] Increased serine protease in stool in IBS-D [43,70,71]
	C reactive protein（CRP）	Higher CRP level compared to healthy control Significant correlation between symptoms and high-sensitivity CRP [72]
	Activity of serum cholinesterase	Increased activity of cholinesterase [73]
	Triggering receptor expressed on myeloid cells 1（TREM-1）	Significant correlation between symptoms and an increase in TREM-1 [74]

Alteration of mucosal barrier function		Increase in mucosal permeability [45,75-79] Enhanced mucosal humoral immunity [80]
Abnormal production of hormones, amines, and peptides	Serotonin (5-HT)	Increase in postprandial serum 5-HT concentration [47,81] and 5-HT_3/5-HT_4 receptors in colonic mucosa [82] Impairment of serotonin transporter (SERT) uptake in platelets [83-85] Improvement of symptoms by 5-HT_3 antagonists [86-88] and 5-HT_4 antagonists [89] Involvement of the CC genotype of tryptophan hydroxylase 1, responsible for serotonin production [90] Sex differences in the involvement of serotonin [88,91,92]
	Chromogranin Secretogranin	An increase in chromogranin and secretogranin in stool is associated with enhanced colon transit time [48]
	Neuropeptide Y（NPY）	Decreased NPY in colonic mucosa [93]
	Leptin	Increased leptin in colonic mucosa [93,94]
	vasoactive intestinal peptide（VIP）	Increased VIP in colonic mucosa [46]
	G protein-coupled estrogen	Increased expression of G protein-coupled estrogen in colonic mucosa [95]

	Neurokinin	Improvement of symptoms by neurokinin receptor antagonists [49]
Bile acid malabsorption		A systematic review using the 75ScHCAT retention test showed that 10% of patients had severe bile acid malabsorption, and 32% had moderate bile acid malabsorption [30] Involvement of variants of the β-klotho gene, which is essential for bile acid homeostasis in colonic transit time in IBS-D [96-99]
Impaired production of short-chain fatty acid		Decrease in acetic acid, propionic acid, total short-chain fatty acid and Increase in n-butyric acid [50]
Impaired gastrointestinal motility function		Enhanced gastric emptying [100] Reduced latency for postprandial colonic pressure increase and enhanced high amplitude propagated contractions [101] Impairment of motility function in small intestine [102,103], colon [51], and rectum [68] Prolonged colon transit time in IBS-C compared to IBS-D [104]
Malabsorption of dietary components		Improvement of intestinal barrier function by gluten-free diet in HLA-DQ2/8 positive patients [52] A sucrase-isomaltase deficiency was observed in 34% of patients diagnosed with IBS-D/M [105]
Impaired autonomic nervous system		Impaired adrenergic sympathetic nervous system [53]

Genomic factors		Involvement of HLA-DQ in the development of IBS-D [54,106,107] Involvement of Rs2349775 (NXPH1) as single nucleotide polymorphisms (SNPs) in the development of IBS-D [55] Involvement of single nucleotide polymorphisms for mitochondrial ATP in the development of IBS-D [108] Involvement of three low-molecular-weight molecules derived from tRNA (tiRNA-His-GTG-001、tRF-Ser-GCT-113、tRF-Gln-TTG-035) in the development of IBS-D [109] Involvement of mutations in the guanylate cyclase C gene in the development of familial diarrhea syndrome [110]